

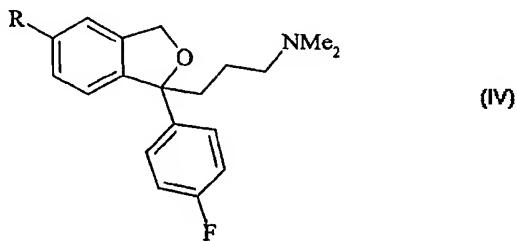
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## (54) Title: sETHOD FOR THE PREPARATION OF CITALOPRAM



## (57) Abstract

Method for the preparation of citalopram comprising reaction of a compound of Formula (IV) wherein R is halogen, or  $\text{CF}_3-(\text{CF}_2)_n-\text{SO}_2-$ , n being 0 to 8, with a cyanide source in the presence of a palladium catalyst and a catalytic amount of  $\text{Cu}^+$  or  $\text{Zn}^{2+}$ , or with  $\text{Zn}(\text{CN})_2$  in the presence of a palladium catalyst.

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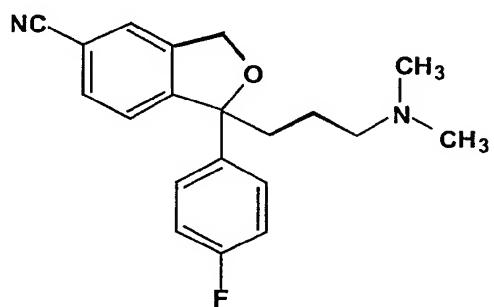
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## Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well known anti-depressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

### Background of the Invention.

Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

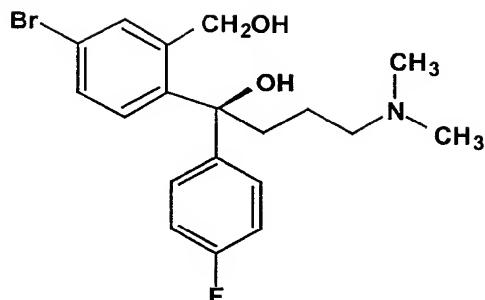
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Citalopram was first disclosed in DE 2,657,271 corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

25 According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

30 According to the method, which is only outlined in general terms, citalopram may be obtained by ring closure of the compound:

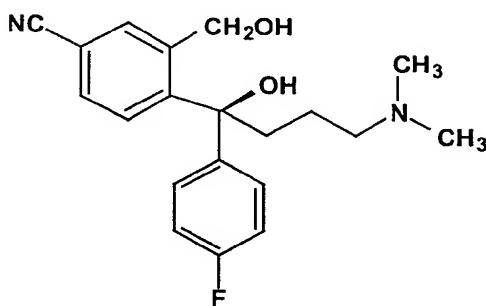
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Formula II

in the presence of a dehydrating agent and subsequent exchange of the 5-bromo group with cyano using cuprous cyanide. The starting material of Formula II is obtained from 5-bromophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium chloride and N,N-dimethylaminopropyl magnesium chloride, respectively.

A new and surprising method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884 according to which an intermediate of the formula



Formula III

is subjected to a ring closure reaction by dehydration with strong sulfuric acid in order to obtain citalopram. The intermediate of Formula III was prepared from 5-cyanophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively.

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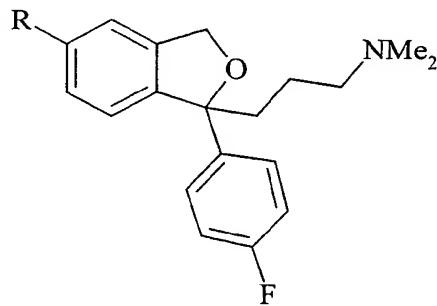
Further processes are disclosed in International patent application Nos. WO 98019511, WO 98019512 and WO 98019513. WO 98019512 and WO 98019513 relate to methods wherein a 5-amino-, 5-carboxy- or 5-(sec. aminocarbonyl)phthalide is subjected to two successive Grignard reactions, ring closure and conversion of the resulting 1,3-dihydroisobenzofuran derivative to the corresponding 5-cyano compound, i.e. citalopram. International patent application No. WO 98019511 discloses a process for the manufacture of citalopram wherein a (4-substituted-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure and the resulting 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran converted to the corresponding 5-cyano derivative which is alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

Finally, methods of preparing the individual enantiomers of citalopram are disclosed in US Patent No 4,943,590 from which it also appears that the ring closure of the intermediate of Formula III may be carried out via a labile ester with a base.

- 5 With respect to the above methods for the preparation of citalopram the process comprising exchange of the 5-bromo group with cyano proved not to be very convenient in commercial scale, since it was the yield was rather low, the product was impure and in particular that it was difficult to separate the resulting citalopram from the corresponding 5-bromo compound.
- 10 It has now been found that citalopram may be obtained in a high yield as a very pure product by a new catalytic process in which 5-cyano is exchanged for a 5-halogen or a 5-triflate group of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran thus avoiding the extensive work up of the old cyanide exchange process.

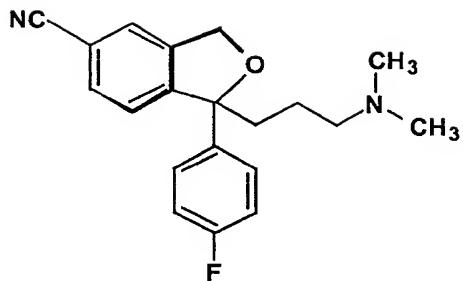
#### 15 Summary of the invention

Accordingly, the present invention relates to a novel method for the preparation of citalopram comprising reaction of a compound of Formula IV



20 Formula IV

wherein R is iodo, bromo, chloro, or  $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2^-$  wherein n is an integer in the range 0-8, incl., with a cyanide source, for example  $\text{KCN}$ ,  $\text{NaCN}$  or  $(\text{R}'_4\text{N})\text{CN}$  where  $\text{R}'_4$  indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched  $\text{C}_{1-6}$  alkyl, in the presence of a palladium catalyst and a catalytic amount of  $\text{Cu}^+$  or  $\text{Zn}^{2+}$ , or with  $\text{Zn}(\text{CN})_2$  in the presence a palladium catalyst, and isolation of the corresponding 5-cyano compound, i.e. citalopram



Formula I

as the base or a pharmaceutically acceptable salt thereof.

- 5 In another aspect, the present invention provides the novel intermediates of Formula IV wherein R is  $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2^-$  wherein n is an integer in the range 0-8 or R is iodo.

In a further aspect the invention relates to the above process in which the compound of Formula IV is the S-enantiomer.

10

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

15

By the process of the invention citalopram is obtained as a pure product in high yield thus reducing costly purification processes. Furthermore, the reaction may be carried out in more convenient solvents, at a low temperature and at a low excess of  $\text{CN}^-$  compared to the known cyano exchange process. The process has environmental advantages in that it only uses small amounts of heavy. Finally, this process gives an improved crystalline product enabling easy conversion to desired salts. The intermediates of Formula IV wherein R is  $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2^-$  wherein n is an integer in the range 0-8 or R is iodo have been found to show pharmacological activity, i.e. 5-HT reuptake inhibiting effects, and accordingly they are useful as antidepressants

25

The cyanide source used may be any useful source. Preferred sources are  $\text{KCN}$ ,  $\text{NaCN}$  or  $(\text{R}'_4\text{N})\text{CN}$  where  $\text{R}'_4$  is as defined above. The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material of Formula IV.  $\text{R}'_4\text{N}^+$  may conveniently be  $(\text{Bu})_4\text{N}^+$ . The cyanide compound is preferably  $\text{NaCN}$  or  $\text{KCN}$  or  $\text{Zn}(\text{CN})_2$ .

30

The palladium catalyst may be any suitable  $\text{Pd}(0)$  or  $\text{Pd}(\text{II})$  containing catalyst, such as  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Pd}(\text{PPh})_2\text{Cl}_2$ , etc. The Pd catalyst is conveniently used in an amount of 1-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu<sup>+</sup> and Zn<sup>2+</sup>, respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 eq. %. Conveniently, about ½ eq. is used per eq. Pd. Any convenient source of Cu<sup>+</sup> and Zn<sup>2+</sup> may be used. Cu<sup>+</sup> is preferably used in the form of CuI and Zn<sup>2+</sup> is conveniently used as the Zn(CN)<sub>2</sub> salt.

5

In a preferred embodiment of the invention, R is CF<sub>3</sub>-(CF<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub><sup>-</sup> wherein n is an integer from the range 0 to 8 or R is bromo or iodo, most preferably CF<sub>3</sub>-(CF<sub>2</sub>)<sub>8</sub>-SO<sub>2</sub><sup>-</sup>, CF<sub>3</sub>-SO<sub>2</sub><sup>-</sup>, bromo or iodo, in particular bromo.

- 10 In another particularly preferred embodiment the compound of Formula IV is reacted with ZnCl<sub>2</sub> in the presence of a Palladium catalyst, preferably Pd(PPh<sub>3</sub>)<sub>4</sub> (tetrakis(triphenylphosphine)palladium).

15 The intermediate of Formula IV wherein R is bromo or chloro may be prepared from bromo- and chlorophthalide, respectively, as described in DE 2,657,271 and the corresponding US 4,136,193. The iodo may be prepared analogously from the corresponding phthalide derivatives and the compounds wherein R is CF<sub>3</sub>-(CF<sub>2</sub>)<sub>n</sub>-SO<sub>2</sub><sup>-</sup> may be prepared from the corresponding hydroxy compounds by a conventional triflation reaction.

- 20 The reaction may be performed in any convenient solvent, preferably acetonitril, propionitrile, THF and ethylacetate.

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

25

- The compound of general Formula I may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, 30 acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

35

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with

an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

5 The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

10 The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

15 Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, 20 preservatives, antioxidants, etc.

### Examples

The invention is further illustrated by the following examples.

25

#### Example 1

##### *Citalopram oxalate*

###### *Method I*

30 A mixture of Zn(CN)<sub>2</sub> (1.2g, 0.01mol) and 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane (6.0g, 0.016mol) in DMF (40mL) was stirred at room temperature under an atmosphere of argon for 30 minutes. Dissolved oxygen was removed by bubbling argon through the reaction mixture for 10 minutes and then tetrakis(triphenylphosphine)palladium (0) (0.8g, 0.0007mol, 4.3mol%) was added. Then the reaction mixture was heated at 75 °C for 3 hrs, poured into water (200mL) and extracted with diethyl ether (2 x 100mL), dried (MgSO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was dissolved in acetone (10mL) and a solution of oxalic acid (0.145g, 0.016mol) in acetone (10 mL) was added with stirring. The citalopram oxalate was isolated by filtration, washed with cold diethyl ether and dried in vacuo to pure citalopram, oxalate (6.1 g, 92 %)

40

**Method 2**

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophtalane (2.5g, 0.007mol), NaCN (0.68 g, 0.014mol), and Zn(CN)<sub>2</sub> (0.014g, 0.00012mol) in THF (40 mL) were stirred at room temperature under an atmosphere of argon for 30 minutes. Then 5 dissolved oxygen was removed by bubbling argon through the reaction mixture before the addition of tetrakis(triphenylphosphine)palladium (0) (0.3 g, 0.0003 mol, 3.7 mol%). Then the reaction mixture was heated at reflux overnight, cooled , diluted with diethyl ether, and then filtered through celite. The filtrate was washed with brine , dried ( $MgSO_4$ ) and concentrated under reduced pressure. The residue was dissolved in acetone (50mL) and a 10 solution of oxalic acid (0.63g, 0.007mol) in acetone (10 mL) was added with stirring. The Citalopram oxalate was isolated by filtration, washed with cold diethyl ether and dried in vacuo to pure citalopram, oxalate (2.4g ,82 %)

**Example 2**

15 *I-(4'-fluorophenyl)-I-(3-dimethylaminopropyl)-5-iodophthalane, oxalate.*

A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (19.3 g, 0.11 mole) and magnesium turnings (2.92 g, 0.12 mol) in dry THF (100 mL), is added dropwise to a suspension of 5-iodophthalide (26.0 g, 0.1 mole) in dry THF (100 mL). 20 The temperature is kept below 0 °C. After the addition is complete, the reaction mixture is stirred for 3 hours at 0 °C.

A second Grignard solution prepared from 3-dimethylaminopropyl chloride (14.6 g, 0.12 mole) and magnesium turnings (3.2 g, 0.13 mole) in dry THF (100 mL) is added to the 25 reaction mixture. The temperature is kept below 0 °C during the addition. After the addition is complete the cooling is removed and the reaction mixture is stirred for an additional 2 hours at ambient temperature.

The reaction mixture is then poured into a mixture of ice water (200 mL) and a saturated 30 solution of NH<sub>4</sub>Cl (100 mL). THF is evaporated in vacuo. Toluene (200 mL) is added and the organic phase is separated and extracted with 1 M HCl (1 x 100 mL). The pH of the water phase is then adjusted to 9 by addition of 25 % NH<sub>4</sub>OH (15 mL) and toluene (100 mL) is added. The reaction is left overnight at room temperature.

The organic phase is separated and 70 % sulfuric acid (10 mL) is added at room 35 temperature. The reaction mixture is stirred at room temperature for 2 hours to complete the ring closure. 25 % NH<sub>4</sub>OH (20 mL) is added and the organic phase is separated, filtered and evaporated in vacuo to give the crude title compound as its free base.

A sample of the crude material (5.0 g, 11.3 mmol) is dissolved in ethyl acetate and filtered through silica. Eluent 1: Ethyl acetate which is discarded. Eluent 2: Ethyl acetate:Triethyl

amine, 95:5 which is collected and evaporated in vacuo to give the title compound (3.5 g, 8.2 mmol) as its free base.

The oxalate salt is precipitated from acetone.

DSC onset: 82 °C and 195 °C. <sup>1</sup>H NMR (DMSO d-6, 250 MHz): 1.3 - 1.65 (2H,m), 2.15

(2H,t, J= 10 Hz), 2.63 (6H,s), 2.87 (2H,t, J= 10 Hz), 5.0-5.2 (2H, 2d, J= 12.5 Hz), 6.5 - 7.05 (2H,s (broad)), 7.16 (2H,t, J= 7.5 Hz), 7.35 (1H,d, J= 8.5 Hz), 7.55 (2H,dt, J= 1.2 Hz, J= 7.5 Hz), 7.64 (1H,d, J= 8.5 Hz), 7.69 (1H,s).

### Example 3

10 *1-(3-Dimethylamino-1-propyl)-1-(4-fluorophenyl)-5-hydroxy-1,3-dihydroisobenzofuran, oxalate*

A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (24,0 g, 0,14 mole) and magnesium turnings (4,38 g, 0,17 mole) in dry THF (80 mL), is 15 added dropwise to a suspension of 5-hydroxyphthalide (10,0 g, 0,07 mole) in dry THF (100 mL) at a temperature below 8°C. The reaction mixture is stirred at room temperature overnight after the addition is finished.

A second Grignard solution prepared from 3-dimethylaminopropyl chloride (8,50 g, 0,07 mole) and magnesium turnings (1,93 g, 0,07 mole) in dry THF (40 mL) and added to the 20 reaction mixture while the temperature is kept below 10°C. The reaction is left stirred overnight.

The reaction mixture is poured into ice water (200 mL) and pH is adjusted to 7 with ammonium chloride water (300 mL) resulting in separation of two phases. The water phase is extracted with ethylacetate (300 mL) and then made basic to pH 8 - 9 with 25% (w/v) 25 ammonium hydroxide. The water phase is extracted with toluene/ethylacetate (3:2, 3x100 mL). The toluene extract is dried over anhydrous sodium sulphate and stirred with charcoal. After filtration the solvent is evaporated in vacuo and the title compound is obtained as a oil (10,2 g, 48%).

5,1 grams (16 mmol) of the obtained oil is dissolved in acetone (25 mL) and treated with 30 anhydrous oxalic acid (1,46 g, 0,016 mole). The mixture is left in the freezer overnight and the precipitated oxalate is filtered off. Yield: 4,77 g

DSC onset 168°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): 1,36 - 1,58 (2H, m), 2,05 - 2,18 (2H, m), 2,63 (6H, s), 2,96 (2H, t, J = 6,5 Hz), 4,95 (1H, d, J = 12,5 Hz), 5,08 (1H, d, J = 12,5 Hz), 6,65 (1H, s), 6,70 (1H, d, J = 8,5 Hz), 7,14 (2H, t, J = 7,5 Hz), 7,24 (1H, d, J = 8,5 Hz) 7,52 (2H, dt, J = 7,5 J = 1,2 Hz), 9 - 10 (2H, broad s).

Anal. calc. for C<sub>21</sub>H<sub>24</sub>N<sub>1</sub>F<sub>1</sub>O<sub>6</sub>: C, 62,20; H, 5,98; N, 3,46.

Found: C, 62,02; H, 5,97; N, 3,42.

**Example 4**

*1-(3-Dimethylamino-1-propyl)-1-(4-fluorophenyl)-5-[(trifluoromethyl)sulfonyl-oxy]-1,3-dihydroisobenzofurane, oxalate.*

- 5    1-(3-Dimethylamino-1-propyl)-1-(4-fluorophenyl)-5-hydroxy-1,3-dihydroisobenzofurane (1,79 g, 5,7 mmol) is dissolved in dichloromethane (35 ml) and cooled in ice/water bath. Under nitrogen trifluoromethane sulfonic acid chloride (0,73 ml, 6,8 mmol) is added dropwise keeping the temperature below 5°C. The reaction mixture is allowed to warm to room temperature overnight. Water (40 mL) and triethylamine (1 mL) are added and the  
10    phases are separated. The water phase is extracted with dichloromethane (25 mL). The combined organic phases are dried over magnesium sulphate and the solvent evaporated in vacuo. The residue (2,09 grams of the title compound as its free base) is dissolved in acetone (10 mL) and treated with anhydrous oxalic acid (0,51 g, 5,7 mmol). After stirring at room temperature overnight the precipitate is filtered off. Yield: 0,84 g, 33%.
- 15    DSC onset 144°C. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz): 1,37 - 1,57 (2H, m), 2,15 - 2,25 (2H, m), 2,61 (6H, s), 2,95 (2H, t, J = 9,4 Hz), 5,12 (1H, d, J = 12,5 Hz), 5,22 (1H, d, J = 12,5 Hz), 7,17 (2H, t, J = 6,3 Hz), 7,42 (1H, d, J = 7,8 Hz), 7,48 (1H, s), 7,59 (2H, dt, J = 6,3 Hz J = 1,2 Hz) , 7,70 (1H, d, J = 7,8 Hz).
- Anal. calc. for C<sub>22</sub>H<sub>23</sub>N<sub>1</sub>F<sub>4</sub>O<sub>8</sub>S<sub>1</sub>: C, 49,16; H, 4,32; N, 2,61.
- 20    Found: C, 49,43; H, 4,36; N, 2,57.

**Example 5**

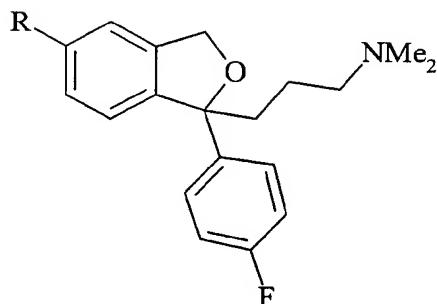
*Citalopram, oxalate, Method 3*

- 25    1-(3-Dimethylamino-1-propyl)-1-(4-fluorophenyl)-5-[(trifluoromethyl)sulfonyl-oxy]-1,3-dihydroisobenzofurane (1,02 g, 2,3 mmol), sodium cyanide (0,22 g, 4,6 mmol), copper iodide (0,05 g, 0,3 mmol) and tetrakis(triphenylphosphine)palladium(0) (0,125 g, 0,1 mmol) are suspended in acetonitrile (10 mL). The suspension is heated at reflux for 5 hours and then  
30    allowed to cool to room temperature overnight with intensive stirring. Ethylacetate (30 mL) is added and the mixture is filtrated on celite. The filtrate is washed with brine (60 mL) and dried over magnesium sulphate before the solvent is removed in vacuo. The crude product is eluted on silica (eluent: ethylacetate, ethanol, triethylamine 75:25:4). Yield: 0,22 g, 30%. The oxalate salt is precipitated from acetone.

## CLAIMS

1. A method for the preparation of citalopram comprising reaction of a compound of Formula IV

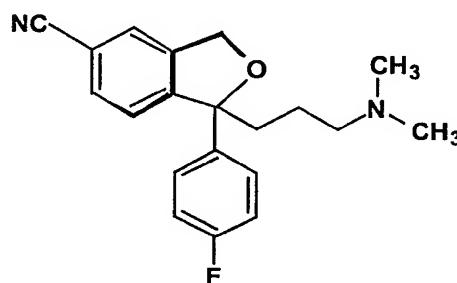
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Formula IV

wherein R is halogen, or  $\text{CF}_3\text{-(CF}_2)_n\text{-SO}_2^-$  wherein n is an integer in the range 0-8, incl., with a cyanide source in the presence of a palladium catalyst and a catalytic amount of  $\text{Cu}^+$  or  $\text{Zn}^{2+}$ , or with  $\text{Zn}(\text{CN})_2$  in the presence a palladium catalyst, and isolation of the corresponding 10 5-cyano compound, i.e. citalopram

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Formula I

as the base or a pharmaceutically acceptable salt thereof.

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2. The method of Claim 1, wherein the cyanide source is  $\text{KCN}$ ,  $\text{NaCN}$  or  $(\text{R}'_4\text{N})\text{CN}$  where  $\text{R}'_4$  indicates four groups which may be the same of different and are selected from hydrogen and straight chain or branched  $\text{C}_{1-6}$  alkyl,

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3. The method of Claim 1 or 2 wherein R is  $\text{CF}_3\text{-(CF}_2)_n\text{-SO}_2^-$  wherein n is an integer from the range 0 to 8, preferably  $\text{CF}_3\text{-SO}_2^-$ .

- 25 4. The method of Claim 1, 2 or 3 wherein R is bromo or iodo.

5. The method of any of Claims 1 - 4 wherein the compound of Formula IV is reacted with  $ZnCl_2$  in the presence of a Palladium catalyst, preferably  $Pd(PPh_3)_4$ .
- 5 6. The method of any of Claims 1 - 5 wherein the cyanide compound used is  $NaCN$ ,  $KCN$  or  $Zn(CN)_2$ .
- 10 7. The method of any of Claims 1 - 4 and 6 wherein the palladium catalyst is  $Pd(PPh_3)_4$ ,  $Pd_2(dba)_3$  or  $Pd(PPh_3)_2Cl_2$ .
- 15 8. The method of Claim 7 wherein the palladium catalyst is  $Pd(PPh_3)_4$ .
9. The method of any of Claims 1 - 8 wherein the reaction is carried out in the presence of a catalytic amount of  $Cu^+$ , preferably in the form of  $CuI$ .
- 10 10. The method of any of Claims 1 - 8 wherein the reaction is carried out in the presence of a catalytic amount of  $Zn^{2+}$ , preferably as  $Zn(CN)_2$ .
- 20 11. A compound of Formula IV
- Formula IV
- wherein R is  $CF_3-(CF_2)_n-SO_2^-$  wherein n is an integer in the range 0-8 or R is iodo.
- 25 12. The method of any of Claims 1 - 10 wherein the compound of Formula IV is the S-enantiomer.
13. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of Claims 1 - 10.